Exhibit B

Mode of delivery and subsequent stress response

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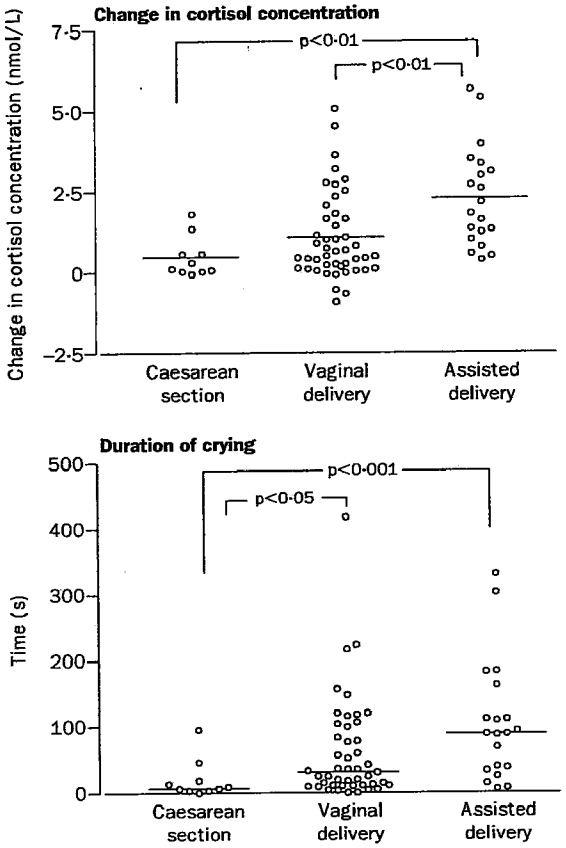
We have shown that a baby's stress (saliva cortisol) and crying response to inoculation at 8 weeks was related to mode of delivery, with the greatest response shown in those born by assisted delivery and the least response in those born by elective caesarean section.

An early experience of pain, neonatal circumcision, has been shown to affect a baby's response to inoculation 4–6 months later, with the baby showing more pronounced pain behaviour than uncircumcised babies.[1] Evidence from animal studies suggests that acute fetal or neonatal stress can set the response of the hypothalamic-pituitary-adrenal (HPA) axis for life.[2] The major stress that most babies experience is birth; babies who undergo elective caesarean section have a less pronounced stress response than those who undergo normal vaginal delivery.[3] Babies delivered by assisted methods (forceps or ventouse) may experience the greatest stress. We suggest that mode of delivery affects subsequent infant responses to stress, as assessed by a rise in saliva cortisol[3] and the duration of crying in response to an injection.[4]

Healthy singleton full-term babies (who had not been circumcised) were studied at a general practice, as they were being given their routine 8-week inoculation by a nurse, while seated on their mother's lap. Consecutive attenders were recruited, and infomed written consent was obtained from each mother, as approved by the institutional ethics committee. Mode of delivery was obtained by parental report and confirmed by hospital computer record. We collected saliva just before, and 20 min after, the injection by giving the infant a dental roll to suck on. The dental roll was then frozen and the saliva cortisol concentration was assessed under masked conditions by a standard radioimmunoassay. Duration of crying was measured by a stopwatch from the time of inoculation, Most of the babies were filmed and a subset of crying times later confirmed by an independent assessor (r=0·94, p<0·0001). The mothers also filled in the Edinburgh postnatal depression scale questionnaire. Data were collected from 46 babies born by normal vaginal delivery, 20 born by assisted delivery (ventouse or forceps), and ten born by elective caesarean. Data from babies born by emergency caesarean were excluded.

Baseline saliva cortisol values were similar in all three groups (normal vaginal delivery mean 1·34 nmol/L [SD 1·34]; assisted delivery 1·18 nmol/L [1·32]; elective caesarean 1·28 nmol/L [1·21]). However, the changes in cortisol values differed significantly (ANOVA, p=0·001; figure). The rise in cortisol was greatest in the assisted delivery group and least in the babies born by elective caesarean. The duration of crying showed a similar pattern (Kruskal-Wallis, p<0·01). Crying time was significantly correlated with change in cortisol concentration (r=0·55, n=76, p<0·001). Maternal Edinburgh postnatal depression scale scores were similar in the different groups, and did not correlate with change in cortisol concentration or crying time.

Our results indicate a link between the method of delivery and a baby's response to inoculation 8 weeks later. They also support the widely held but anecdotal view that babies born by assisted delivery can continue to be difficult to soothe. The degree of stress and



Mean changes in cortisol concentration and duration of crying according to mode of delivery

p values for change in cortisol concentration are for unpaired tests after Bonferroni's correction; p values for duration of crying are for Dunn's multiple comparison test.

pain experienced at delivery may thus control the later response. However, other mediating mechanisms, such as the length of second stage, degree of fetal distress, or the effect on the baby of the mother's response to a difficult birth, may also be involved.

There is increasing evidence that the set of the HPA axis is important in subsequent diseases such as depression.[4] In addition, obstetric difficulties, including mode of delivery, are known risk factors for later psychopathology.[5]

1 Taddio A, Katz J, Lane Ilersich A, Koren G. Effect of neonatal circumcision on pain response during routine vaccination. *Lancet* 1997; **349**: 599–603.

2 Meaney M, Bhatnager S, Diorio J, et al. Molecular basis for the development of individual differences in the hypothalamic-pituitary-adrenal stress response. *Cell Mol Neurobiol* 1993; **13**: 321–47.

3 Lewis M, Thomas D. Cortisol release in infants in response to inoculation. *Child Dev* 1990; **61**: 50–59.

4 Checkley S. The neuroendocrinology of depression. *Br Med Bull* 1996; **52**: 597–617.

5 Dalman C, Allebeck P, Cullberg J, Grunewald C, Koster M. Obstetric complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. *Arch Gen Psychiatry* 1999; **56**: 234–40.

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